CONJUCHEM

Montreal, May 18, 2005

Commissioner of Patents
International Preliminary Examination Authority
Box PCT
5 Place Ville-Marie, Suite 700
Montreal, Quebec H3B 2G2

Sir :

RESPONSE TO THE FIRST WRITTEN OPINION

RE: **International PCT Patent Application**
No PCT/CA2004/001409
Title : LONG LASTING INSULIN DERIVATIVES AND METHODS THEREOF
Inventors : Dominique P. Bridon et al.
Applicant : ConjuChem Inc.
Examiner: Colleen MacFarlane
Our ref : 3210 PCT

This is responsive to the first Written Opinion dated November 19, 2004.

Please note that a new appointment of agent in favor of France Leclaire, as well as a Demand for an International Preliminary Examination are concurrently filed.

The deadline for responding to the Written Opinion is **May 25, 2004**.

Applicant hereby submits new pages of the description and a new set of claims. The Examiner is respectfully requested to enter this amendment before examining the application. For the Examiner's convenience, a table resuming the modifications brought to the claims as well as explanations concerning the support for such modifications is found in Annex. Applicant respectfully submits that no new matter has been added. The pages to be replaced are the following:

Please enter the present amendment under Article 34 with respect to the above-mentioned application.

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Description

Delete page 1 presently on file, and insert new pages 1 and 1A submitted herewith.

Claims

Delete claims 1 to 38, and insert the new set of 36 claims submitted herewith.

Remarks

Claims 1 to 36 are now in the application

The claims have been amended so as to better define Applicant's invention. In particular, it has been specified in claim 1 that the reactive group is selected from the group consisting of an α,β-unsaturated carbonyl moiety, a succinimidyl-containing group and a maleimido-containing group. In other words, claim 1 has been amended so as to include the limitations of claims 3 and 4. Therefore, claims 3 and 4 have been deleted since being redundant. Consequently, original claims 5 to 38 have been renumbered as new claims 3 to 36.

Applicant respectfully submits that none of prior art references cited by the Examiner teaches nor suggests an insulin derivative as defined in new claim 1. Therefore, new claim 1 is novel and non-obvious over the cited documents. At least in view of their dependency, new claims 2 to 36 are also believed to be novel and non-obvious over the cited documents.

Novelty (Box No. V)

The Examiner's objections to claims 1-3, 7, 16-23, and 33-38 as lacking novelty have been considered but are respectfully contested for the following reasons.

As previously indicated, claim 1 has been amended so as to include the subject matter of claims 3 and 4. Since the novelty of original claim 4 has already been recognized by the Examiner in the Written Opinion dated November 19, 2004, new claim 1 is thus not anticipated by the prior art. Therefore, new claim 1 as well as new claims 2 to 36 depending therefrom are also believed to be novel. In fact, Applicant respectfully submits that none of the cited documents teaches nor

suggests an insulin derivative, which comprises an insulin molecule and a reactive group (i.e. α,β-unsaturated carbonyl moiety, a succinimidyl-containing group or a maleimido-containing group) for covalently bonding a blood component.

In view of the above, the Examiner is respectfully requested to withdraw her rejection of claims 1-3, 7, 16-23, and 33-38 as lacking novelty.

Inventive step (Box No. V)

The Examiner's objections to claims 1-23 and 33-38 as failing to demonstrate an inventive step have been considered but are respectfully contested for the following reasons.

Applicant would like first to point out to the Examiner that the insulin derivative of the present invention would be understood by a person skilled in the art as being an exogenous insulin derivative comprising a reactive group, which can be covalently bonded to a blood component. One of the main advantages provided by such a covalent bonding is that the derivative will have a long-lasting effect. Applicant respectfully submits that none of the prior art references cited by the Examiner teaches nor suggests such an insulin derivative.

D1 describes insulin or a functional derivative equivalent thereof, which is covalently linked to a pendant molecular group. As mentioned on page 9, lines 16-20, the pendant molecular group has an affinity for a binding protein. However, it is clearly stated on page 7, lines 33 to 37 "Binding of the pendant molecular group and the binding protein is not covalent. Binding forces may be for instance electrostatic (e.g. attraction of opposite charges, hydrogen bonding) or hydrophobic." Applicant would like to put the emphasis on the fact that it is well know in the present art that the term "binding" refers to a non-covalent interaction between entities as previously described, while a covalent bond is made by the covalent "bonding" of two entities. Therefore, it is apparent that D1 clearly teaches away Applicant's invention which benefits from the covalent bonding between the insulin derivative and a blood protein.

In D2 for which some of the inventors and Applicants are the same than in D1, the invention relates a compound comprising an insulin molecule covalently bonded to 3,3',5' triiodothyronine. As previously stated for D1, insulin is thus not covalently bonded to a blood protein but is rather reversibly binding to a circulating protein such as albumin, as specified on page 1, lines 14, 15, 36 and 37. Moreover, D2 is silent about a reactive group as

defined in new claim 1. Therefore, as previously mentioned for D1, D2 teaches away Applicant's invention.

D3 discloses acylation of insulin at position B29 for binding to serum albumin. Such a binding affinity is, as previously indicated in D1, a non-covalent relationship. In fact, insulin, via a fatty acid added by means of acylation, is binding to albumin. Such a binding is not a covalent bonding but rather electrostatic or hydrophobic forces which are not permanent as explained in D1 on page 7, lines 33 to 37. Therefore, it seems clear that D3 fails to teach an insulin derivative, which has a reactive group for covalently bonding to a blood component such as albumin.

D4 discloses an insulin conjugate, in which 3 or 4 insulin molecules are conjugated to a polymer, carboxymethyl dextran (CMD). However, this document fails to disclose an insulin derivative comprising a reactive group as defined in new claim 1, and which permits the insulin derivative to be covalently bonded to a blood component.

D5 relates to stimulators of insulin release and not to insulin derivatives like Applicant's invention. The differences between the actions of these two classes of compounds (insulin-releasing compounds (i.e. insulinotropic) and insulin derivatives) result in important differences between the needs that these compounds satisfy or the problem to be solved by these compounds.

While a long-lasting insulinotropic (as in D5) encourages release of the patient's endogenous insulin in response to stimuli, this insulin's duration of action is naturally restricted to a few hours. The need that such an insulinotropic compound satisfies is thus to allow or enhance release of endogenous insulin by pancreatic cells in response to a stimuli during a long period of time.

On the contrary, a long-lasting insulin, which is an exogenous insulin, (as in the present invention) will be present in the body over a long period of time during which it will continuously perform its insulin action. The need that such a long-lasting insulin satisfies is to supplement or replace insufficient continuous basal release of endogenous insulin. For instance, the present invention is suitable for the treatment of Diabetes of type I, which is characterized by the fact that the beta cells of pancreas are destroyed by immune reaction and cannot express insulin or be stimulated to do so. Therefore, the invention of D5 would not be appropriate for the treating Diabetes of Type I.

Thus, a person skilled in the art would clearly consider these two needs to be fundamentally different and thus would not have been led to the insulin derivative of new claim 1 by considering the teaching of D5.

D6 describes conjugates comprising insulin which is covalently attached to monosaccharidic derivatives or PEG derivatives. However, this document fails to suggest that the conjugates can be covalently bonded to a blood component. Moreover, this document is silent about the reactive groups mentioned in new claim 1.

D7, similarly to D6, describes insulin derivatives comprising insulin, which is covalently bonded to glycosides or to PEG derivatives. Such a document also fails to describe insulin derivatives adapted to be covalently bonded to a blood component or the reactive groups used in applicant's invention.

D8 discloses alkanedioic acid derivatives of insulin. However, this document fails to teach insulin derivatives adapted to be covalently bonded to a blood component. This document is also silent about the reactive groups described in applicant's invention.

D9 discloses N-acylated O-substituted derivatives. This document also fails to disclose insulin derivatives having a reactive group as defined in new claim 1.

In view of the above, it seems apparent that the person skilled in the art would not have been led directly and without difficulty to the Applicant's derivative of new claim 1 by considering the above-mentioned documents. In fact, it must be reminded that none of these documents proposes a solution with respect to providing a long-lasting effect to insulin by preparing an insulin derivative that has such a long-lasting activity. For instance, D5 proposes to solve a completely different problem, which is to provide a long-lasting stimulators that will generate endogenous insulin release. Therefore, claim 1 as well as dependent claims 2 to 36 depending therefrom are believed to have an inventive step over the prior art.

The Examiner is thus respectfully requested to withdraw her rejection of claims 1-23 and 33-38 as lacking inventive step.

Correction of certain defects in the international application (Box No. VII)

The description has been amended so as to comply with Rules 5.1(a)(ii) and 5.1(a)(iii) PCT. In particular, a section concerning prior art and comments concerning the technical problem to be solved have been added on page 1 and 1A.

Modification brought in view of certain observations on the international application (Box No. VIII)

The dependency of claim 12 (new claim 10) has been modified so as to depend upon claim 8 (new claim 6), which comprises appropriate antecedent for the term "linker".

In view of the foregoing amendment, Applicant respectfully submits that new claims 1 to 36 are novel and inventive and that they comply with Article 6 of PCT. Applicant also submits that the description is also in compliance with PCT Rules. Therefore, the Examiner is respectfully requested to reconsider the application as presently amended, and to send to the Applicant a favorable International Preliminary Report on Patentability.

Respectfully submitted,

ConjuChem Inc.

Signed by LECLAIRE, France
Patent Agent of ConjuChem Inc.

ANNEX

New claims	Support
1	original claims 1, 3 and 4
2	original claim 2
3	original claim 5
4	original claim 6
5	original claim 7
6	original claim 8
7	original claim 9
8	original claim 10
9	original claim 11
10	original claim 12
11	original claim 13
12	original claim 14
13	original claim 15
14	original claim 16
15	original claim 17
16	original claim 18
17	original claim 19
18	original claim 20
19	original claim 21

New claims	Support
20	original claim 22
21	original claim 23
22	original claim 24
23	original claim 25
24	original claim 26
25	original claim 27
26	original claim 28
27	original claim 29
28	original claim 30
29	original claim 31
30	original claim 32
31	original claim 33
32	original claim 34
33	original claim 35
34	original claim 36
35	original claim 37
36	original claim 38